REMARKS

Claims 1-23 were pending in the application. Claims 1, 9, 18, 19, 20, 22, and 23 have been amended and claim 8 has been canceled, without prejudice. Claims 24-34 have also been canceled, without prejudice, as being directed to a non-elected invention. Accordingly, after the amendments presented herein have been entered, claims 1-7 and 9-23 will remain pending.

Support for the amendments to the claims may be found through the specification including the originally filed claims. No new matter has been added.

The specification has been amended to insert SEQ ID NOs, where appropriate, including the locations indicated by the Examiner at paragraph 8 of the Office Action. Additionally, the specification has been amended to replace the original sequence listing with a substitute sequence listing that includes the additional sequences noted by the Examiner at paragraph 8 of the Office Action. A computer-readable form of the sequence listing is also being submitted herewith. The content of the substitute paper and computer readable copies of the sequence listing are the same and include no new matter, as required by 37 C.F.R. 1.825(a) and (b).

Any amendments to and/or cancellation of the claims should in no way be constructed as acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate applications(s).

Objection to the Specification

The Specification has been objected to by the Examiner because at page 6, line 37 of the specification, the U. S. Patent Application No. is left blank. Furthermore, the Examiner has requested that the parent application data in the specification at page 1 be updated.

Applicants submit that the foregoing informalities have been corrected and, thus, the foregoing objections have been rendered moot. Accordingly, Applicants respectfully request that they be reconsidered and withdrawn.

Rejection of Claims 1-23 under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-23 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> [t]he instant claims recite 'a method for identifying a compound that binds to a target and the method comprising; a) forming a first library comprising a multiplicity of peptides; b) selecting from the library at least one peptide that binds to the target;...' Thus, the claimed method after step b) a compound (peptide) that binds to the target is already identified. Thus, it is not clear what does applicants [sic] mean by the reset [sic] of the method steps.

Applicants respectfully submit that the aforementioned rejection has been rendered moot in view of the amendments to the claims. Specifically, independent claims 1, 22, and 23, have been amended to recite a "non-peptide compound." Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

Furthermore, with regard to the term "non-peptide compounds," the Examiner is of the opinion that the "[c]laims recite that the second library comprises 'non-peptide compounds.' The specification definition or explanation of 'non-peptide compounds' seem to be confusing." In particular, the Examiner alleges that

> [t]he specification discloses in page 2, that "the non-peptide library comprises compounds that, while not peptides, are structurally related to peptides, such as peptide analogues, peptide derivatives and or peptidomimetics...." However, the term 'non-peptide' is vague because according to the definition they are not peptides, but analogues of peptides or derivatives of peptides. It is not clear how the peptide analogues and derivatives are not peptides. Applicants are requested to clarify. The 'non-peptide' compounds in the instant claims are considered as compounds which do not have any natural and unnatural amino acids present in them. The small organic [heterocyclic] compounds or antibiotics would be considered as non-peptide compounds according to the instant claims or only peptide compounds with certain amino acids replaced by synthetic amino acids is

> considered as non peptides, it is not clear. If applicants mean that the non-peptide compounds are peptide compounds with certain amino acids replaced by synthetic amino acids, applicants are requested to clearly recite them as peptide compounds with unnatural amino acids.

Applicants respectfully traverse the aforementioned rejection and submit that the term "non-peptide" is clear and definite when read in light of Applicants' specification. Specifically, Applicants direct the Examiner to the specification at page 8, line 30 through page 9, line 11 where the term "non-peptide compounds" are defined as follows:

> ***[t]he term "non-peptide compounds," as used herein, is intended to include compounds comprising at least one molecule other than a natural amino acid residue, wherein the structures of the compounds cannot be determined by standard sequencing methodologies but rather must be determined by more complex chemical strategies, such as mass spectrometric methods.*** Preferred non-peptide compounds are those that, although not composed entirely of natural amino acid residues, are nevertheless related structurally to peptides, such as peptidomimetics, peptide derivatives and peptide analogues. (***Emphasis added***).

Applicants also respectfully submit that the term "peptide" is differentiated in the specification at page 4, lines 4 through 14 as follows:

> [t]he term "peptides," as used herein with regard to libraries, is intended to include molecules comprised ***only*** of natural amino acid residues (*i.e.*, alanine, arginine, aspeartic acid, asparagines, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenyalanine, praline, serine, threonine, tryptophan, tyrosine and valine) linked by peptide bonds, or other residues whose structures can be determined by standard sequencing methodologies (*e.g.*, direct sequencing of the amino acids making up the peptides or sequencing of nucleic acid molecules encoding the peptides). The term "peptide" is ***not intended to include*** molecules structurally related to peptides, such as peptide derivatives, peptide analogues or peptidomimetics, whose structures cannot b determined by standard sequencing methodologies but rather must be determined by more complex chemical strategies, such as mass spectrometric methods.

(***Emphasis added***).

Based on the aforementioned definitions in Applicants' specification, it is evident that the term "non-peptide compounds" refers to compounds comprising at least one molecule other than a natural amino acid residue. Thus, Applicants respectfully submit that the metes and bounds of the term "non peptide compound" are clear and definite to one skilled in the art. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

With regard to claim 4, the Examiner has requested that the term "anchor library" be clarified. Applicants respectfully submit that the term "anchor library" is well known in the art and described at page 7, line 1 through line 10 of the specification as follows:

> [t]he term "anchor library" refers to a peptide library in which the peptides have non-continuous regions of random amino acids separated by specifically designated amino acid residues. Anchor libraries are therefore subsets of a complete library of a specified length. Anchor libraries can be used to identify essential contacts between a ligand and a target, and have the advantage that only a subset of all possible peptides need be synthesized and screened. In a preferred embodiment, an anchor library is made up of peptides about 16 amino acids long. An anchor library can be prepared by genetic means (*e.g.*, by synthesizing a multiplicity of nucleic acid molecules encoding a multiplicity of anchor peptides) or by chemical means (*e.g.*, by directly synthesizing a multiplicity of anchor peptides).

Applicants respectfully submit that based on the foregoing definition provided in the specification the metes and bounds of an "anchor library" are clear and definite. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

With regard to claim 8, the Examiner alleges that the claim is indefinite by "reciting 'wherein step c) comprises determining the nucleotide sequence of a nucleic acid molecule or

molecules that encode the at least one peptide. Claim 1 step c) recites method for determining the sequence or sequences of the at least one peptide that binds to the target." In particular, the Examiner alleges that "[i]t is not clear how determining the peptide sequence in step c) comprises determining nucleotide sequence. The method steps for determining the nucleotide sequence of the peptide [are] not the same as the method steps for determining the peptide sequences."

While in no way acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting prosecution, Applicants have canceled claim 8, thereby rendering the aforementioned rejection moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

With regard to claim 9, the Examiner alleges that that limitation "the amino acid sequence" has insufficient antecedent basis in the claim or in claim 1. Applicants respectfully traverse this rejection and submit that there is antecedent basis in amended claim 1, which recites in step c) "determining the ***amino acid sequence or sequences*** of the at least one peptide that binds to the target, thereby generating a peptide motif." (*Emphasis added*). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

With regard to claims 10 and 11, the Examiner believes that these claims are vague and indefinite because of the recitation of the terms "peptide derivative" and "peptide analogue." In particular, the Examiner is of the opinion that "[c]laim 1 in step d) recites that forming a second library comprising non-peptide compounds. Thus, it is not clear what does the applicants mean in claim 10, peptide derivative. It is not clear what the meets and bound of the term 'derivative,' does applicants mean modified peptides. Further, the peptide derivatives doe not include the non-peptide compounds of claim 1." The Examiner is also of the opinion that

> it is not clear what are the meets and bound of the term 'peptide analogues,' does the applicants mean that the peptide analogues are different from peptide derivatives. Further it is not clea[r] how peptide analogues are not peptides. Claim 1 in step d) recited that forming a second library comprising non-peptide compounds.

> Thus it is not clear what does applicants mean in claim 11, peptide analogue.

Applicants respectfully traverse the aforementioned rejection on the grounds that the terms "peptide derivative" and "peptide analogue" are clear and definite in view of the teachings in Applicants' specification. In particular, Applicants respectfully submit that the term "derivative" is defined in the specification at page 8, line 36, through page 9, line 2 as follows:

> a "derivative" of a compound X (*e.g.*, a peptide) refers to a form of X in which one or more reactive groups on the compound have been derivatized with a substituent group. Examples of peptide derivatives include peptides in which an amino acid side chain, the peptide backbone, or the amino- or carboxy-terminus has been derivatized (*e.g.*, peptidic compounds with methylated amide linkages).

The term "analogue" is also defined in the specification at page 9, lines 2-6 as follows:

> an "analogue" of a compound X refers to a compound which retains chemical structures of X necessary for functional activity of X yet which also contains certain chemical structures which differ from X. An examples of an analogue of a naturally-occurring peptide is a peptides which includes one or more non-naturally-occurring amino acids.

Applicants respectfully submit that based on the aforementioned definitions provided in the specification the metes and bounds of a "peptide derivative" and a "peptide analogue" are clear and definite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

With respect to claim 21, the Examiner alleges that "it is not clear how the third library of compounds are different from the second library of compounds." Furthermore, the Examiner is of the opinion that "[a]ccording to the claims the first library is a peptide library and the second library is non-peptide library, and it is not clear how the third library is different from the

non-peptide library of the second library. Does [sic] applicants mean that the structure of a compound identified from [sic] second library is modified to derive a third library. Applicants are requested to clarify."

Applicants respectfully traverse this rejection and submit that the third library is described on page 11, lines 28 through 37 as follows:

> [t]he skilled artisan will appreciate that the compound or compounds identified from the second library can be used as a basis for forming further libraries that can be used for further screening of the target. That is, the information gained from the screening of the second library can be used to design another motif, for example a modified peptide motif (*e.g.*, a motif based on the structure of peptide derivatives, peptide analogues and/or peptidomimetics), and a subsequent, third library can be formed comprising compounds designed based on the motif generated from the screening of the second library. The target is then screened with the third library and active compounds identified as previously described herein. This process can be repeated until a compound with a desired binding affinity for the target is obtained.

Accordingly, Applicants respectfully submit that the skilled artisan reading the foregoing teachings in Applicants' specification would be able to clearly differentiate between the second and third library. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, second paragraph rejection.

Rejection of Claim 21 Under 35 U.S.C. §112, first paragraph

The Examiner has rejected claim 21 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled din the relevant art that the inventor(s), at the time application was filed, had possession of the claimed invention." Specifically, the Examiner is of the opinion that

> [t]he instant claim 21 briefly recites methods for forming a third library based on the selected non-peptide compounds identified from the second library....The instant specification discloses methods of identifying a peptidomimetic which binds to a target. The specificating method discloses that a first peptide library is screened for binding of target, and using the identified compound a peptidomimetic or displacing some of the natural amino acids with synthetic amino acids a second library is formed. And the second library is screened for identifying compounds that bind a target. The specification examples are drawn to a phage display library of peptides as a first library and replacing some of the amino acids of the identified compound which binds to the target from the first library with synthetic amino acids to prepare the second library, and methods of screening the second library for binding with the target.

Furthermore, the Examiner alleges that

> [t]he specification description is directed to specific peptide compounds which specifically bind to LHRH-R and modifying by replacing certain amino-acids in the identified peptide to generate second library which clearly do not provide an adequate representation regarding the method of generating the third library of compounds made by the presently claimed invention.

Applicants respectfully traverse the foregoing rejection on the grounds that Applicants' specification contains a sufficient description of the method of claim 21 to inform one of skill in the art that Applicants were in possession of the claimed invention at the time of filing, as required by 35 U.S.C. §112 (see M.P.E.P. §2163). As indicated above, Applicants' specification provides that the compound or compounds identified from the second library can be used as a basis for forming further libraries that can be used for further screening of the target (see, *e.g.*, page 11, lines 28 through 37 of the specification). As also taught in Applicants' specification, the third library may be generated using the same methods used to generate the second library. Based on the foregoing teachings in Applicants' specification, the skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing.

Moreover, Applicants respectfully submit that working examples are not required to be present in a specification for the "written description" requirement of the 35 U.S.C. §112 to be satisfied (See M.P.E.P. §2164.02).

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, first paragraph rejection.

Rejection of Claims 1, 3- 4, and 9-12 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3- 4, and 9-12 under 35 U.S.C. §103(a) as being unpatentable over Hirshmann *et al.* [JACS 114(24): 9699-9701] in view of Blake (5,565,325). The Examiner relies on Hirshmann *et al.* for teaching "the synthesis of non-peptide libraries of peptido-mimetics based upon known peptide ligand (motif) structures" and for teaching "the identification of compounds from the library which bind to the target." The Examiner is of the opinion that "the structure of a known peptide motif can be used as the basis of a non-peptide library." Also, the Examiner admits that "Hirshmann *et al.* do not teach the formation of a first peptide library to identify the structure of a peptide ligand or a motif that binds the target molecule (receptor)."

The Examiner further relies on Blake for teaching "a method of screening peptide libraries to identify peptides that bind to target receptors and to optimize ligand sequences by varying the residues at non-essential positions." In particular, the Examiner is of the opinion that

> Blake teach that the peptide libraries can be made by the method of Merrifield synthesis (solid support bound methods)...Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify the peptide motif as taught by Blake and use the motif in the method of Hirshmann et al for identifying a non-peptide compound that binds to a target, since Hirshmann et al teaches that the structure of a known peptide motif can be used as the basis of a non-peptide library.

The Examiner has Failed to Provide the Necessary Motivation to Impel One of Ordinary Skill in the Art to Make Applicants' Invention

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

Claims 1, 3-4, 9-12 are directed to methods for identifying a non-peptide compound that binds to a target. The method involves forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery,*

804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to identify a non-peptide compound that binds to a target by forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims.

First, the primary reference relied on by the Examiner, namely, Hirshmann *et al.*, teaches methods for synthesizing ***steroidal peptidomimetics*** that are recognized by a targeted endocrine receptor. Hirshmann *et al.* teach that "the steroid nucleus can serve as a scaffold for the attachment of mimics" (page 9700, second column, last two lines). Hirshmann *et al.* do not teach or suggest the formation of libraries, nor do they teach or suggest methods for forming a first library comprising a multiplicity of ***peptides***; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims.

Moreover, the secondary reference of Blake does not make up for the deficiencies of the primary reference. Specifically, Blake teaches "methods for determining the amino acid

sequence of peptides which bind to a ligand of interest from a large mixture of random or semi-random peptides" (column 2, lines 33-36). Blake does not teach or suggest forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims.

Furthermore, it is Applicants position that the teachings of the cited references relied upon by the Examiner to combine the references are legally insufficient to provide the requisite motivation. With regard to the necessary legal standard, Applicants refer the Examiner to *Arkie Lures v. Larew Tackle*, 119 F.3d. 953, (Fed. Cir. 1997). In *Arkie Lures*, the Larew invention was directed to a "salt-impregnated fishing lure." In that case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known, [and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination." The CAFC continued that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." Id at page 957.

The court further stated that:

> No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . ***.It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements***. Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination.

(Emphasis added)

Id at pages 957 and 958.

Similar to the situation in the *Arkie Lures* case, the teachings of the cited references alone or in combination are ***insufficient*** to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention. The Examiner argues that the motivation would arise from the teachings of Blake to identify a peptide motif for a target of interest and the teachings of Hirshmann *et al.* for developing non-peptide libraries. These general statements directed to the separate elements of the claimed invention fail to provide a specific teaching or suggestion which would motivate the ordinarily skilled artisan to make a ***non-peptidic secondary library based on peptide motif identified by screening of a primary peptide library***, as required by Applicants' claims. Moreover, it is Applicant's position that the motivation relied upon by the Examiner, which is not based on explicit suggestions within the cited references, but rather on what the Examiner argues that one of ordinary skill in the art would have known, is legally insufficient to establish the requisite suggestion to combine references.

In further support of their position, Applicants point to the recent CAFC decision in *In re Rouffet* (*In re Rouffet*, Lexis 16414 (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Staellite Communications System" (Ruddy).

In *Rouffet* the Court of Appeals found that:

> ***[b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make***

> ***the combination, this court infers that the examiner selected these references with the assistance of hindsight.*** This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d. 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. (*Emphasis added*).

In re Rouffet at [*17].

Similarly, it is Applicants' position that since the Examiner has selected prior art references which teach methods for synthesizing steroidal peptidomimetics that are recognized by a targeted endocrine receptor (Hirshmann et al.) and methods for determining the amino acid sequence of peptides which bind to a ligand of interest from a large mixture of random or semi-random peptides (Blake), and has not pointed to any teaching or suggestion in the art that would impel the ordinarily skilled artisan to modify the cited art to arrive at Applicants' invention, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.'" *Smith Kline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d. 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

Additional support of the position that the claimed invention is unobvious is found in *In re Vaeck* (*In re Vaeck* 947 F.2d 488. (Fed. Cir. 1991)) where the CAFC upheld the nonobviousness rejections of a biotechnology invention. In *Vaeck* the invention was drawn to "a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the Bacillus genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the Bacillus gene in a host cyanobacterium, so as to produce the desired insecticidal protein (footnote omitted)." *Id* at page 490. The prior art (a total of eleven references) was applied in various combinations against the claims. The primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene

encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. The secondary references taught, *inter alia,* "expression of genes encoding certain *Bacillus* insecticidal proteins" in other host cells; "the initiation specificities *in vitro* of DNA-dependent RNA polymerases purified from two different species of cyanobacteria (footnote omitted);" and "a host-vector systems for gene cloning in the cyanobacterium." *Id* at page 491. The Examiner's position was that:

> it would have been obvious to one of ordinary skill in the art to substitute the Bacillus genes [which had been expressed in heterologous hosts in the teachings of the prior art] for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the Bacillus genes in the transformed cyanobacteria. The Examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

Id at page 492.

The CAFC disagreed with the Examiner's position and found that the teachings of the prior art cited in *Vaeck* were not sufficient to support the interchangeability of bacteria and cyanobacteria as host organisms for the expression of heterologous insecticidal proteins. The court stated that "there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria." *Id* at page 493. The court further stated that while the prior art disclosed "expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts. . . . [w]hile it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. *Id* at pages 493 and 494.

The CAFC contrasted its findings in *In re Vaeck* with those in *In re O'Farrell* stating "[i]n contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." In *O'Farrell* the invention was directed to a "method for producing a predetermined protein in a stable form in a transformed host species of bacteria." *In re O'Farrell* 853 F.2d 894. 1988. 7 U.S.P.Q. 2d (BNA) 1673. The prior art (Polisky) taught a previous attempt to "control the expression of cloned heterologous genes inserted into bacteria." *Id* at page 899. The prior art differed from the claim at issue, however, because it taught a method of expressing "a segment of DNA from a frog that coded for ribosomal RNA," which is normally not translated into protein. Although ribosomal RNA is not normally translated into protein, the court found that in the prior art publication by Polisky the authors were "obviously interested in using their approach to make heterologous proteins in bacteria." *Id* at page 900. The CAFC referred to the Polisky paper which stated:

> In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of Xenopus [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Id at page 900 (quoting from Polisky *et al.* at page 4904).

The court stated that "[t]he authors of the Polisky paper ***explicitly pointed out*** that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a 'fused protein' consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain." *Id* at page 901. The court also referred to a passage in the Polisky reference, where the authors stated that "[i]f an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a

functional eukaryotic polypeptide." Id at page 901 (quoting from Polisky *et al.*). The court upheld the PTO decision that the claims in *O'Farrell* were obvious over Polisky because:

> ***virtually everything in the claims was present in the prior art.*** . . . The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. . . .Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, 'a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide.' ***Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.*** (Emphasis added).

Id at 901.

It is Applicants' position that, as in *In re Vaeck*, there is no teaching, neither explicit nor implicit, in any of the references cited by the Examiner, which would have impelled one of ordinary skill in the art to make the instantly claimed invention. ***The art cited by the Examiner is directed to individual elements of Applicants' invention, and not to the invention as a whole*** (Hirshmann *et al.* teach methods for synthesizing steroidal peptidomimetics and Blake teaches methods for determining the amino acid sequence of peptides). Given the standard for obviousness set forth by the CAFC, it is Applicants' position that the Examiner has improperly relied on hindsight obtained from Applicants' invention in making the combination of references cited.

Applicants' Unexpected Results Further Demonstrate That The Examiner Has Failed To Establish A *Prima Facie* Case Of Obviousness

Even assuming *arguendo* that a *prima facie* case of obviousness were established by the Examiner, (which Applicants dispute), the nonobviousness of the invention is apparent from the results achieved when the invention is put into practice. "One way for an Applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results', *i.e.*, to show that

the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.23d 746, - 34 USPQ2d 1684 (Fed. Cir. 1995). (See M.P.E.P §716.02(a)). Furthermore, and the "[p]resence of a property not possessed by the prior art is evidence of nonobviousness." (See M.P.E.P §716.02(a) citing *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)).

Use of the claimed invention as described in the specification, allows for the identification of compounds that bind to a target that by use of peptide libraries with the use of chemically based libraries such that the advantages of each are maintained while the disadvantages of using either approach alone are overcome. The claimed invention has unexpectedly superior properties over the prior art because the skilled artisan can identify compounds that bind to a target by use of both peptide based and chemically based libraries while maintaining the advantages of each. This advantage demonstrates that the claimed invention possess properties that were not previously possessed by the prior art. It is, therefore, apparent that the actual results obtained through use of the instantly claimed invention are not predicted from (*i.e.*, are unexpected over) the teachings of the prior art.

Based on the cited references, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that this section 103(a) rejection is improper and request that it be reconsidered and withdrawn.

Rejection of Claims 1, 3- 7, and 9-15 and 18-20 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3- 7, 9-15, and 18-20 under 35 U.S.C. §103(a) as being unpatentable over Hirshmann *et al.* [JACS 114(24): 9699-9701] in view of Blake (5,565,325) and Gordon *et al.* (J. Medicinal Chemistry. Vol. 37, no. 10, 1385-1401, 1994). The Examiner relies on Hirshmann *et al.* and Blake for the reasons stated above. The Examiner relies on Gordon *et al.* for teaching "that the library as large as 10^{12} members as indicates that large libraries (10^{12}-10^{6} compounds) are useful in lead identification and intermediate size libraries are useful in chemical analoging and small libraries (10^{2} or less are useful for fine tuning (i.e., see figure 1 and 19 and associated test.)" Furthermore, the Examiner is of the opinion that "Gordon also teach that [the] libraries of [peptide] meimetics are known in the art

(*i.e.*, peptoids figure 4) which can be interpreted as peptide analogues and/or peptide derivatives. In addition the reference teaches that the identification of compounds with modest or high affinity from the libraries is well known in the art."

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for at least the following reasons. First, the Hirschmann *et al.* and the Blake references, cited by the Examiner, fail to teach or suggest forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, for the reasons set forth above with regard to the section 103(a) rejection of claims 1, 3, 4, and 9-12.

Moreover, the Gordon *et al.* reference fails to make up for the aforementioned deficiencies in the Hirschmann *et al.* and the Blake references. Gordon *et al.*, teach methods for creating ***peptide*** combinatorial libraries and library screening strategies. Gordon *et al.* do not teach or suggest methods for forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on a peptide motif that is identified by screening a primary library***, as required by Applicants' claims. Rather, Gordon *et al.* only disclose, in a very general manner, that initial peptide leads identified in random library screening, "can serve as starting points for creating secondary recombinant ***peptide*** libraries or as leads for refinement by synthetic chemical combinatorial methods" (see Gordon *et al.*, page 1395, 1st column, lines 3-6). This statement fails to provide the necessary motivation for the ordinarily skilled artisan to make a ***non-peptidic secondary library based on peptide motif identified by screening of a primary peptide library***, as required by Applicants' claims.

Based on the cited references, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that this section 103(a) rejection is improper and request that it be reconsidered and withdrawn.

Rejection of Claims 1, 3- 4, 9-12 and 16-17 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3- 4, 9-12 and 16-17 under 35 U.S.C. §103(a) as being unpatentable over Hirshmann *et al.* [JACS 114(24): 9699-9701] in view of Blake (5,565,325) and Stankova *et al.* (Drug Development Research. Vol. 33, pages 146, 1994). The Examiner relies on Hirshmann *et al.* and Blake for the reasons stated above. The Examiner relies on Stankova *et al.* for teaching "the use of tandem mass spectroscopy for analysis of structure of compounds identified from library."

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for at least the following reasons. First, the Hirschmann *et al.* and the Blake references, cited by the Examiner, fail to teach or suggest forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, for the reasons set forth above with regard to the section 103(a) rejection of claims 1, 3, 4, and 9-12.

Furthermore, the secondary reference (Stankova et al.), relied on by the Examiner does not make up for the above stated deficiencies in the Hirschmann *et al.* and the Blake references. Specifically, Stankova *et al.* disclose screening non-peptide libraries by mass spectroscopy but do not disclose forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby generating a peptide motif; forming a

second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims. Moreover, as indicated above, the unexpected results achieved by use of the claimed invention demonstrate the non-obviousness of the invention.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw this section 103(a) rejection of claims 1, 3-4, 9-12 and 16-17.

Rejection of Claims 1, 3- 4, 8-12, 16-17, and 22-23 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3-4, 8-12, 16-17, and 22-23 under 35 U.S.C. §103(a) as being unpatentable over Hirshmann *et al.*, Blake, Stankova *et al.*, and further in view of Scott *et al.* (Science, vol. 249, 386-390, 1990). In particular, the Examiner is of the opinion that

> Hirshmann et al teach the synthesis of non-peptide libraries of peptidomimetics based upon known peptide ligand (Motif). The reference teaches that the identification of the compounds from the library which bind to the target. As the synthetic paths of the compound since the library are known, Hirshmann et al are able to determine the structure of the non-peptide library members.
>
> Blake et al teaches a method for screening for peptide library to identify peptide that bind to target receptors and to optimize ligand sequences by varying the residues at non-essential positions. Blake teaches that the peptide libraries can be mad using Merrifield synthesis (solid support bound) methods.

The Examiner further relies on Stankova *et al.* for teaching "the use of tandem mass spectroscopy for analysis of structure of compounds identified from a library and on Scott *et al.* for teaching "that the sequence of peptide ligands having affinity for a target molecule in phage display epitope library can be deduced by screening the library and then determining sequence of the phage nucleic acid which encodes the peptides. Scott *et al.* teach a hexapeptide library."

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for at least the following reasons. Applicants reiterate the substance of the remarks set forth above with respect to the section 103(a) rejection of claims 1, 3-4, 9-12, and 16-17. Briefly, the Hirschmann *et al.*, the Blake, and the Stankova *et al.* references, cited by the Examiner, fail to teach or suggest forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby ***generating a peptide motif***; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target.

Furthermore, the secondary reference (Scott *et al.),* relied on by the Examiner does not make up for the above stated deficiencies in the primary references. Specifically, Scott *et al.* teach that the sequence of the peptide can be deduced from the determined DNA sequence of the carrier phage, but do not disclose forming a first library comprising a multiplicity of peptides; selecting from the first library at least one peptide that binds to the target; determining the sequence or sequences of the at least one peptide that binds to the target, thereby generating a peptide motif; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target. Moreover, the unexpected results achieved by use of the claimed invention demonstrate the non-obviousness of the invention.

In summary, Applicants respectfully submit that ***none of the prior art references alone or in combination*** teach or suggest Applicants' invention. In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw this section 103(a) rejection of claims 1, 3-4, 8-12, 16-17, and 22-23,

Provisional Rejection of claims 1-23 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-23 under the judicially created doctrine of obvious-type double patenting. In particular, the Examiner is of the opinion that "[c]laims 1-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 12-20, 22-26, 41-53 of copending Application No. 08/769,250."

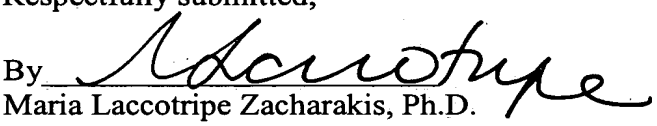
Applicants respectfully submit that when the pending claims in the present application are indicated as allowable, Applicants will consider submitting, if appropriate, a terminal disclaimer complying with 37 C.F.R. §1.321 (b) and (c). The filing of this terminal disclaimer should in no way be construed as acquiescence to the Examiner's obviousness-type double patenting rejections and will be done solely to expedite the prosecution of the application.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617-227-7400).

Dated: September 19,2003

Respectfully submitted,

By 

Maria Laccotripe Zacharakis, Ph.D.
Limited Recognition Under 37 C.F.R. § 10.9(b)
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant